

### **Remarks**

Applicants respectfully request entry of the Amendment and reconsideration of the claims.

Applicants have amended claim 6 with support at page 10, lines 1-11. Please cancel claim 11 without prejudice. Applicants reserve the right to file one or more continuation applications to claim the cancelled subject matter.

Applicants respectfully request reconsideration and withdrawal of the pending rejections under 35 U.S.C. §§ 102(b) and 103(a).

#### **Rejection under 35 U.S.C. § 102(b)**

The Examiner rejects claims 6 and 8 under 35 U.S.C. § 102(b) as allegedly anticipated by Robak et al. (*Pol. J. Pharmacol.*, 47, 63-67 (1995)). A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applicants respectfully traverse this rejection.

Applicants have amended claim 6 where the hepatic glutathione increasing compound and the hepatic nitric oxide donor are independently bound to albumin or a bile salt. Robak & Gryglewski do not disclose a composition comprising a hepatic glutathione increasing compound and a hepatic oxide donor bound to albumin or a bile salt. For at least this reason, the cited art does not disclose each and every element of the instant claims. In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

#### **Rejection under 35 U.S.C. § 102(b)/§ 103(a)**

The Examiner rejects claims 6, 8, and 11 under 35 U.S.C. § 102(b) as allegedly anticipated by, or in the alternative, obvious under § 103(a) over Kondo et al. (*FEBS Lett.*, 413, 236-238 (1997)). Applicants respectfully traverse.

***1. Anticipation.*** A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); *See also*, MPEP §2131.

The Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the prior art. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original); MPEP § 2112. To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citations omitted); MPEP § 2112.

Applicants respectfully assert that Kondo et al. do not disclose a pharmaceutical composition comprising all of the required elements. The Examiner asserts that the claimed composition is disclosed in Figure 3. Specifically, the Examiner contends that the experimental mixture of human erythrocytes incubated with peroxynitrite in the presence of glutathione or N-acetylcysteine, wherein serum albumin is inherently present, anticipates claims 6 and 8. Applicants respectfully disagree.

Applicants respectfully assert that serum albumin is not inherently present. To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Figure 3 and the methods at 2.1 disclose that the composition is a suspension of human erythrocytes in saline. This is not whole blood where serum albumin would necessarily be present. To arrive at erythrocytes in saline, erythrocytes were separated from plasma and resuspended in physiological saline. During the separation, serum albumin would be separated out (along with the platelets, neutrophils, etc.). From Kondo et al.'s description of the erythrocyte suspension in saline. Extrinsic evidence has not been provided to demonstrate that serum albumin was necessarily present.

As currently amended, claim 6 requires that the hepatic glutathione increasing compound and the hepatic nitric oxide donor are independently bound to albumin or a bile salt. Kondo et al. have not disclosed glutathione, N-acetylcysteine, or SIN-1 bound to albumin or a bile salt. Thus, Kondo et al. do not disclose each and every claim element.

The Examiner contends that Kondo et al. disclose a composition comprising SIN-1 since SIN-1 *could be* the source of the peroxynitrite for the composition disclosed in Figure 3. First, inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999); MPEP § 2112. “Could be” is not sufficient to establish inherency. Thus, it is not inherent that SIN-1 produced the peroxynitrite. Second, the composition comprises peroxynitrite and not SIN-1. It is irrelevant whether SIN-1 was the source of the peroxynitrite. Sources of compounds in a composition do not establish anticipation. Anticipation requires each and every claim element as arranged in the claim. The claim does not recite peroxynitrite. SIN-1 is not present in the erythrocyte composition with glutathione or the N-acetylcysteine. As Kondo et al. explain at page 237, column 2, SIN-1 was incubated with erythrocytes but did not produce much hemolysis. Thus, SIN-1 was not useful for the experiments described in Figure 3. The authors then chose peroxynitrite, which produced the desired hemolysis, to incubate with various antioxidants to study their effects. Thus, Kondo et al. do not disclose each and every claim element.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

**2. Obviousness.** To establish a *prima facie* case of obviousness, the teachings of the prior art should have suggested the claimed subject matter to the person of ordinary skill in the art, and all the claim limitations must be taught or suggested in the references cited by the Examiner. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). As articulated by the Supreme Court, a combination is obvious if it is no more than the predictable use of known elements according to their established functions; and there was a reason to combine the known elements. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. \_\_\_, 127 S. Ct. 1727 (2007). To make a *prima facie* case of obviousness, “it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.” *Id.* Applicants submit that the Examiner does not make a *prima facie* case of obviousness since all the limitations of the present claims are not taught by Kondo et al.

Applicants respectfully assert that Kondo et al. do not teach or even suggest all of the claim elements. Kondo et al. may discuss many of the claim elements (although not all), but

does not put them together into a single pharmaceutical composition. Nor is there a suggestion or any reason to combine some of the compounds. An obviousness rejection where the relied upon references teach that all the aspects of the claims were individually known is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. MPEP § 2143.01(III); *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993); See also *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000).

Kondo et al. tested the effects of antioxidants on the hemolysis of erythrocytes. To achieve hemolysis, Kondo et al. incubated peroxynitrite with human erythrocytes in saline in the presence or absence of, *inter alia*, N-acetylcysteine and albumin. Kondo et al. also explicitly taught away from including SIN-1 (a claimed nitric oxide donor) in these erythrocyte suspensions since it did not produce much hemolysis in preliminary experimentation. As discussed above, Kondo et al. used erythrocytes separated from plasma so that serum albumin would have been removed. Thus, Kondo only teaches a hepatic glutathione increasing compound in a suspension or albumin in suspension. Kondo et al. do not disclose or even suggest a combination of the hepatic glutathione increasing compound (N-acetylcysteine) with a nitric oxide donor (as the Examiner suggests SIN-1), or that each of these compounds are actually bound to the albumin. For at least these reasons, Applicants respectfully assert that the Examiner has not provided cited art to demonstrate or suggest a composition as instantly claimed. In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

#### **Rejections under 35 U.S.C. § 103(a)**

The Examiner rejects claims 6, 8-10, 12-13, 16-17, 21-25 and 31 under 35 U.S.C. § 103(a) as allegedly obvious over Robak et al. (1995) as applied to claim 6 and 8 above, in view of WO 00/19992 (Lautt) and further in view of Mattia et al., *Diabetologia*, 41: 1392-1396 (1998).

To establish a *prima facie* case of obviousness, the teachings of the prior art should have suggested the claimed subject matter to the person of ordinary skill in the art, and all the claim limitations must be taught or suggested in the references cited by the Examiner. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). As articulated by the Supreme Court, a combination is

obvious if it is no more than the predictable use of known elements according to their established functions; and there was a reason to combine the known elements. *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007). A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. MPEP § 2141.02(VI); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Applicants respectfully assert there was no reason to combine the art cited by the Examiner and the cited art does not teach or suggest all of the claim elements.

Applicants contend that there is no motivation to combine Robak & Gryglewski (1995) with WO 00/19992 (Lautt). The Robak article discloses experimental solutions of SIN-1 with cysteine and SIN-1 with N-acetylcysteine. The results of the mixture of SIN-1 with cysteine and N-acetylcysteine in solution were the consumption of sulfhydryl groups of cysteine and N-acetylcysteine (pages 65-67) and generation of nitrites. Thus SIN-1 broke down the compounds of cysteine and N-acetylcysteine by destroying these sulfhydryl groups.

WO 00/19992 discloses a nitric oxide donor to increase insulin sensitivity. The Examiner asserts at p. 11 of the office action that “the idea of combining two compounds [SIN-1 and N-acetylcysteine] in a composition logically flows as they have been known to possess the property of reducing insulin resistance individually in [the] prior art.” Applicants contend that the Robak article teaches away from combining SIN-1 with cysteine or N-acetylcysteine. One would not look to provide a pharmaceutical composition with a combination of compounds where one compound attacks the other compound’s sulfhydryl groups. Applicants respectfully assert that it logically flows to specifically not combine SIN-1 with N-acetylcysteine. Since the Robak article teaches away from the combination as a pharmaceutical composition, Applicants respectfully assert that there is no motivation to combine the cited art.

Additionally, claim 6 has been amended to require that the hepatic nitric oxide donor and the hepatic glutathione increasing compound be bound independently to albumin or a bile salt. None of the Robak article, WO 00/19992, and Mattia et al. article disclose binding compounds to

albumin or a bile salt. For at least this reason, the cited art does not teach or suggest all or the claimed elements. In view of the foregoing, Applicants respectfully request removal of this rejection.

2. *Vitek et al.* The Examiner rejects claims 6 and 8 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 6,436,996 (Vitek et al.). Applicants respectfully assert the '996 patent does not disclose or suggest all of the claim elements. As currently amended, claim 6 requires each of the hepatic glutathione increasing compound and the nitric oxide donor to be bound independently to albumin or a bile salt. The '996 patent does not teach or suggest that any of the compounds to be administered should be bound to albumin or a bile salt. For at least this reason, the '996 patent does not disclose or suggest all of the claim elements.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a).

## Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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